THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 89

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SADAO OIDA, AKIRA YOSHIDA,
YAWARA TAJIMA, and NORIKO TAKEDA

Appeal No. 94-4265
Application 08/035,915[1]

ON BRIEF

Before WILLIAM F. SMITH, WEIFFENBACH and WALTZ, ***Administrative Patent Judges***.

WEIFFENBACH, ***Administrative Patent Judge***.

[1] Application for patent filed March 23, 1993. According to applicants, this application is a continuation of Application 07/935,642, filed August 25, 1992, now abandoned; which is a continuation of Application 07/810,304, filed December 19, 1991, now abandoned; which is a continuation of Application 07/697,532, filed April 30, 1991, now abandoned; which is a continuation of Application 07/481,717, filed February 15, 1990, now abandoned; which is a continuation of Application 07/018,794, filed February 19, 1987, now abandoned; which is a continuation of Application 06/873,856, filed June 11, 1986, now abandoned; which is a continuation of Application 06/742,132, filed June 6, 1985, now abandoned; which is a continuation of Application 06/525,616, filed August 22, 1983, now abandoned.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 37, 39, 43, 45-48, and 50-59, the only claims remaining in the application. We reverse.

The Claimed Subject Matter

The claims on appeal are directed to a process for preparing azetidinone and carbapenem derivatives. Claim 51 is illustrative of the claimed subject matter and is appended to this decision.

The Prior Art

The following prior art references are relied upon by the examiner in support of the rejection of the claims:

Oki et al (Oida III[2])	Japanese Kokai 57-9784	Jan. 19, 1982
Morimoto (EP 45198)	European Patent Application 0 045 198	Feb. 3, 1982

The following additional references, not relied upon in the stated rejection of the claims on appeal, are cited by the examiner in the answer and the appellants in their reply brief:

International Tables for X-ray Crystallography, "Volume II Mathematical Tables," The Kynoch Press, Birmingham, England, pp. 60-64 (1959) (reply brief, appendix 4).

Handbook of Chemistry and Physics, The Chemical Rubber Co., 46th Edition, p. F-121

[2] Although Oida is the second named inventor in the Japanese Kokai, the examiner identified the reference by "Oida III" early in the prosecution. Although it is customary for the Board to identify a reference by the last name of the first named inventor only, since the examiner and appellants have used "Oida III" throughout the prosecution, we will use it for the sake of consistency. The reference has been translated and it is the translation which has been relied upon by the examiner and by us in our decision.

(1965) (answer, p. 2).

Pine et al., *Organic Chemistry*, 4th Edition, McGraw-Hill International Book Company, pp. 79-82 (1981) (reply brief, appendix 2).

Pfaendler et al., "Structure, Reactivity, and Biological Activity of Strained Bicyclic $-Lactams," *J. Am. Chem. Soc.*, Vol. 103, pp. 4526-4531 (1981) (reply brief, appendix 3).

Allen et al., "The Development of Versions 3 and 4 of the Cambridge Structural Database System," *J. Chem. Inf. Comput. Sci.*, Vol. 31, pp. 187-204 (1991) (reply brief, appendix 5).

The Rejection

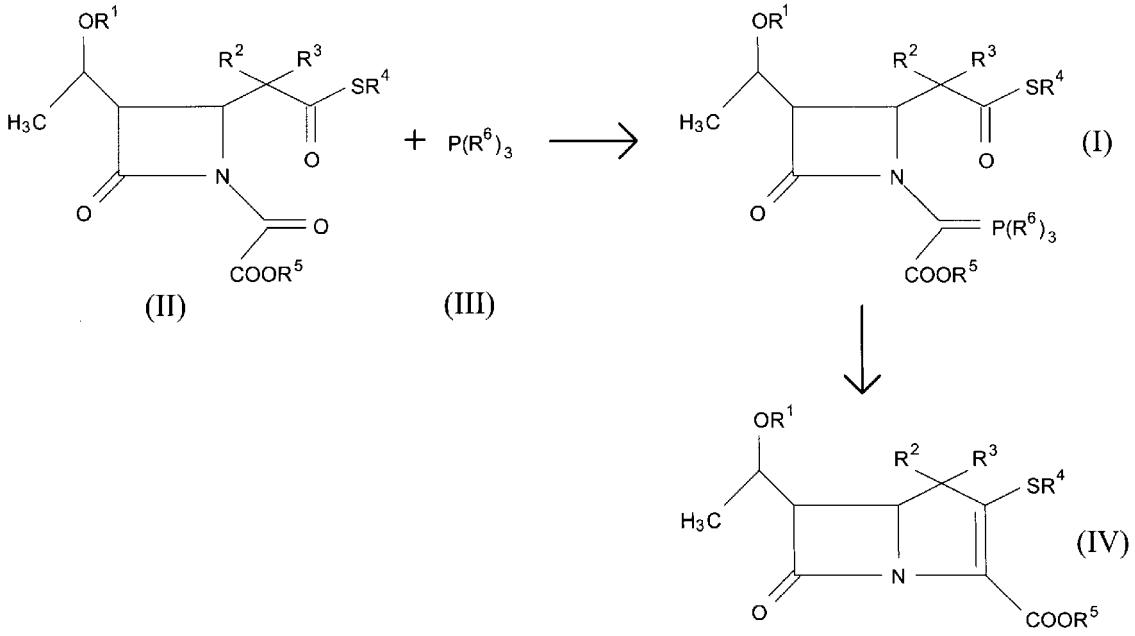
All of the claims stand rejected under 35 U.S.C. § 103 as being obvious in view of either Oida III or EP 45198.[3]

Opinion

We have carefully considered the respective positions advanced by appellants and the examiner. For the reasons set forth below, we will not sustain the examiner's rejection.

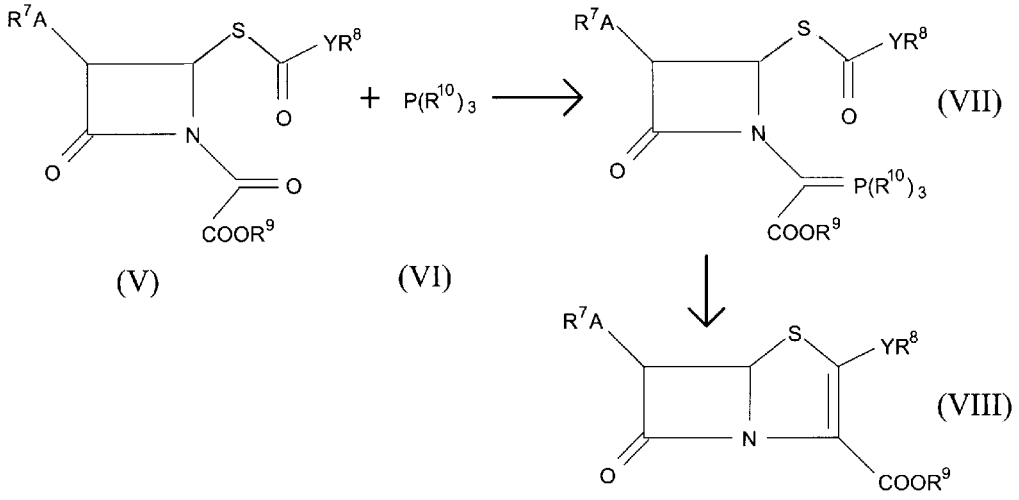
In essence, appellants' process involves forming an azetidinone derivative which is then cyclized by "conventional means," a Witting condensation reaction, to form a carbapenem derivative having formula (IV) as per the following reaction mechanism:

[3] We note that in the final rejection, the examiner made separate rejections of the claims over Oida III and EP 45198, but combined them into a single rejection in the examiner's answer.



wherein R^1 can be, *inter alia*, hydrogen; R^2 and R^3 may be the same or different and each may be hydrogen, a C_1-C_6 alkyl group or a phenyl group; R^4 is, *inter alia*, a C_1-C_6 alkyl group; R^5 is, *inter alia*, a carboxy-protecting group; and R^6 is, *inter alia*, a C_1-C_6 alkoxy group or a phenoxy group. The method defined by claim 50 comprises cyclizing the compound of formula (I) to form the compound of formula (IV). The method of claim 51 is essentially the reaction mechanism illustrated above, but without identifying the compound having formula (I) as an intermediate. Claim 48 is dependent on claim 51 and specifies that the method of claim 51 is effected without isolation of the intermediate product (presumably the compound of formula (I)) produced by the reaction of compounds having formulae (II) and (III).

Oida III teaches a method of producing penemve-3-carboxylic acid derivatives in accordance with the following reaction mechanism:



wherein R^7 can be a hydroxy group, A can be ethylidene, R^8 can be a C_1-C_5 alkyl group, and R^9 is a carboxy protecting group, R^{10} can be an alkoxy group, and Y can be a methylene group or sulfur atom[4] (Oida III, pp. 4-7). The examiner's position is that a methylene group (Y) and the sulfur atom bridging the carbonyl group and the nitrogen ring in the Oida III compounds (formulae (V-VIII)) are known structural isosteres, i.e. the methylene group (Y) is interchangeable with the sulfur atom. The examiner relies on *Mead Johnson v. Premo Pharmaceutical Labs*, 207 USPQ 820 (D.N.J. 1980) to support his position.

[4] The examiner appears to hold that Oida III teaches a "Y" as being only a methylene group. However, as translated, the reference states on pages 2 and 6 that "Y represents an oxygen atom, sulfur atom, or methylene group."

We agree with appellants that the *Mead* case does not support the examiner's position. In the *Mead* case, the court made a factual finding that

> 44. The only difference between the structure of isoxsuprine and that of nylidrin is that isoxsuprine contains an oxygen atom adjacent to the right-hand phenyl group or benzene ring whereas nylidrin has a methylene group (CH_2) attached to the benzene ring instead of the oxygen atom in the same position.

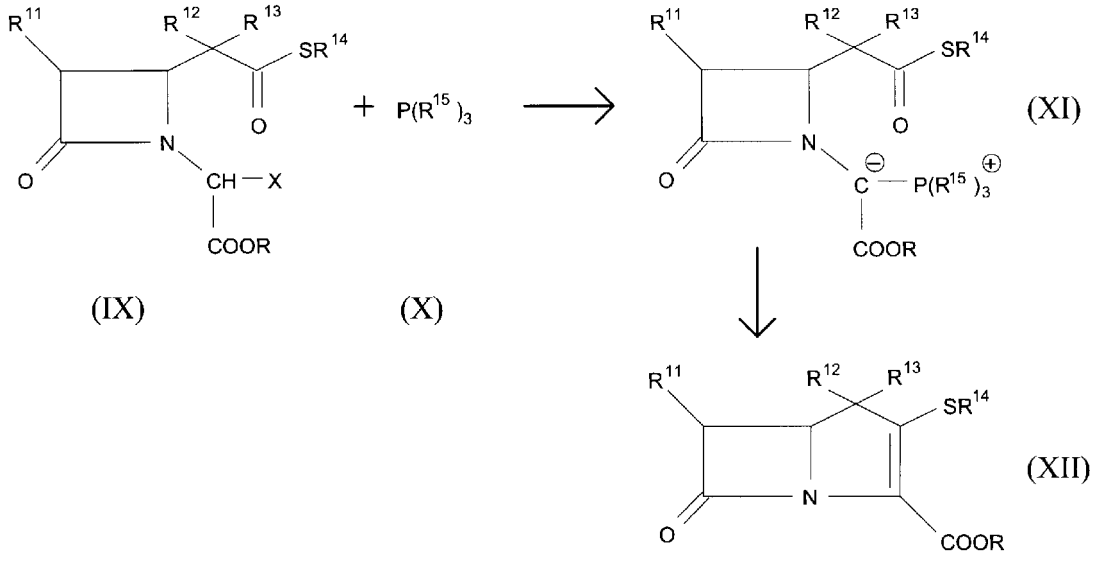
The court considered testimony and other evidence before it and concluded that

> 87. One of the many classical molecular modifications, in accordance with the principles of bioisosterism, is the replacement a methylene group with an oxygen atom in biologically active compound. Such substitution was well known prior to 1955 to produce compounds of similar biological activity to the lead compound, and it would have been obvious for a medicinal chemist in that time period to have made the substitution when seeking to modify a compound containing a methylene group, provided, of course, that the substitution was chemically feasible in that particular position.
>
> 88. In terms of the priority which a medicinal chemist would have accorded to the isosteric replacement of oxygen for methylene in the nylidrin compound prior to 1955, a medicinal chemist would have considered that modification to be the second out of four which would logically have been attempted in the search for an improved cardiovascular drug.
>
> 89. Another theory known in the organic chemistry art prior to 1955 which posited that oxygen and methylene could be interchanged in compounds without greatly affecting their physical properties was Grimm*s Hydride Displacement Law ....
>
> 90. Oxygen was said by Grimm to be interchangeable with the methylene group. The modification of nylidrin which resulted from the interchanging of oxygen and methylene was within the replacement rules taught by Grimm, although Grimm*s law does not postulate any compounds which specifically related to isoxsuprine or nylidrin.
>
> 91. A medicinal chemist seeking in 1955 to modify the compound nylidrin in order to improve its biological properties would have been motivated to substitute oxygen for methylene adjacent to phenyl in nylidrin because of the teachings of the

> prior art as to the interchangeability of oxygen and methylene and the fact that substitution had produced compounds of similar and sometimes improved activity.

We do not find in the record before us that the examiner has established that sulfur and methylene in the Oida III compounds are isosteres. Drawing a conclusion from the *Mead* case that sulfur and methylene are isosteres because evidence in *Mead* led the judge to conclude that oxygen and methylene are isosteres for compounds such as nylidrin and isoxsuprine without any further evidence is pure speculation. The examiner has not presented any evidence that sulfur and methylene isosterism is known in the art for the claimed compounds and that such interchange would have been considered to be within the skill of the art. The court in the *Mead* case based its decision on isosterism on evidence. Here the examiner has provided no such evidence. The examiner is in error in relying on the *Mead* case to establish isosterism rather than presenting scientific reasoning to show that Oida III's and appellants' compounds are isosteric compounds. *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996). Furthermore, the examiner's reliance in this case on *In re Durden*, 763 F.2d 1406, 226 USPQ 359 (Fed. Cir. 1985) and *In re Albertson*, 332 F.2d 379, 141 USPQ 730 (CCPA 1964) to support a conclusion of obviousness is also misplaced. *See In re Ochiai*, 71 F.3d 1565, 1569-1572, 37 USPQ2d 1127, 1131-1133 (Fed. Cir. 1995). For these reasons, we will not sustain the rejection of any of the claims over Oida III alone.

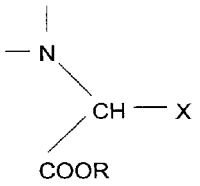
The examiner rejected all of the claims as being unpatentable under 35 U.S.C. § 103 over EP 45198 alone. The reference is directed to preparing carba-2-penem compounds having formula (XII) made in accordance with the following reaction mechanism:



wherein R^{11} can be a hydroxyalkyl group, R^{12} can be an alkoxycarbonyl group, R^{13} can be a C_1-C_4 alkyl group or aryl group, R^{14} can be a C_1-C_4 alkylthio group, R^{15} can be a lower alkoxy group, X is a halogen atom or a reactive ester residue, and COOR is a protected carboxyl group (EP 45198: p. 2, line 4 to p. 3, line 1; p. 5, lines 8-29; p. 10, line 24 to p. 11, line 4; p.18, line 24 to p. 19, line 3).

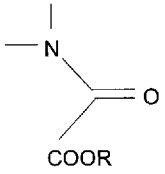
The reaction mechanism in EP 45198 is similar to appellants' claimed mechanism, the principle differences being substituent R^{12} at the 1-position of the penem structure and the starting compound (formula (IX)) for the reaction. While appellants' R^3 and R^{13} in EP 45198 can be a C_1-C_4 alkyl group or phenyl, appellants' R^2 and R^{12} in EP 45198 are different. Appellants' compound defines R^2 as being hydrogen, a C_1-C_8 alkyl group or a phenyl group while EP 45198 defines R^{12} as being, for example, a C_1-C_4 alkoxycarbonyl group or a C_1-C_4 alkylcarbonyl (EP 45198: p. 5, lines

8-13). As for the other noted difference, EP 45198 has the following functional group in starting formula (IX):



(XIII)

while the functional group in appellants' starting formula (II) is



(XIV)

The examiner has not made out a *prima facie* case of obviousness over EP 45198 taken alone. The examiner has not presented a reasoned analysis to explain why the teachings of EP 45198 would have led one skilled in the art to appellant's claimed starting compound having formula (II). EP 45198 does not disclose R^{12} as comprising moieties as set forth set forth in appellants' claims for R^2. While we note that EP 45198 discloses on page 2 that carba-2-penems are known having no substituents or two methyl groups at the 1- position,[5] the reference does not disclose making compounds using the Wittig reaction where R^{12} is hydrogen or a methyl group. The examiner has not presented any reasoned analysis to explained how it would have been obvious to one skilled in the

[5]Upon the return of this application to the examining group, the examiner should consider the references cited on page 2 of EP 45198.

art from the teachings of EP 45198 for R^{12} to be hydrogen, a C_1-C_8 alkyl group or a phenyl group as required by appellants' claims on appeal. For the foregoing reasons, we will not sustain the rejection of the claims over EP 45198 alone.

In summary, we find that the examiner has not established a *prima facie* case of obviousness for the claimed subject matter over Oida III or EP 45198. Accordingly, the decision of the examiner is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	))))) BOARD OF PATENT
CAMERON WEIFFENBACH Administrative Patent Judge	) APPEALS AND) INTERFERENCES)))
THOMAS A. WALTZ Administrative Patent Judge	))

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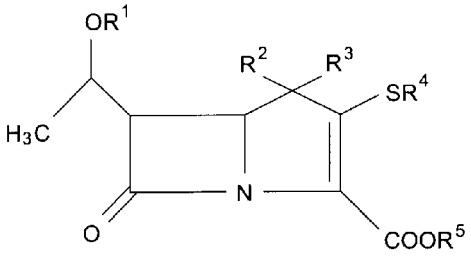
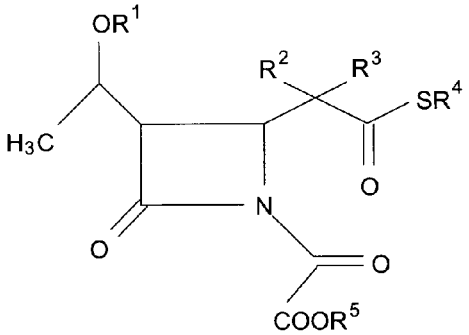
APPENDIX

51. A process for preparing a compound of the formula (IV):



(IV)

which comprises reacting a compound of the formula (II):



(II)

with a compound of the formula (III):

(III)

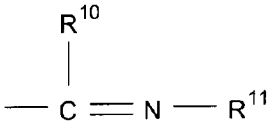
and cyclising the product of this reaction to prepare said compound of the formula (IV);
wherein

R^1 represents hydrogen or a hydroxy-protecting group;

R^2 and R^3 may be the same or different and each represents hydrogen, a C_1-C_8 alkyl group or a phenyl group;

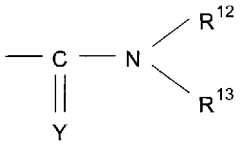
R^4 represents a C_1-C_6 alkyl group;

a non-aromatic heterocyclic group having from 4 to 8 ring carbon atoms and having one or two ring nitrogen atoms and optionally containing an oxygen atom, a sulphur atom, a sulphinyl group, a sulphonyl group or a carbonyl group, and optionally having one or more substituents attached to the carbon atoms or to any nitrogen atom, selected from the group consisting of (1) substituents for attachment to the ring carbon atoms selected from the group consisting of C_1-C_6 alkyl groups, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl groups, C_2-C_8 alkoxyalkyl groups, methoxycarbonylmethyl, ethoxycarbonylmethyl, t-butoxycarbonylmethyl, benzyloxycarbonylethyl, methoxycarbonylpropyl groups, C_2-C_7 cyanoalkyl groups, C_1-C_6 haloalkyl groups, C_1-C_6 alkoxy groups, halogen atoms, C_1-C_6 aliphatic acyloxy groups, C_1-C_6 aliphatic acylamino groups, cyano group, azido group, carboxy group, C_2-C_7 alkoxycarbonyl groups, carbamoyl group, C_1-C_6 alkylthio groups, C_1-C_6 alkylsulphinyl groups, C_1-C_6 alkylsulphonyl groups, nitro group; and (2) substituents for attachment to said ring nitrogen atom(s) selected from the group consisting of C_1-C_6 alkyl groups, C_2-C_6 alkenyl groups, C_2-C_6 alkynyl groups, C_3-C_8 cycloalkyl groups, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, 3-cyclopentylpropyl, 2-cyclopentylpropyl, 3-cyclohexylpropyl, 2-cyclohexylpropyl, 4-cyclopentylbutyl, 3-cyclohexylbutyl, phenyl, naphthyl groups, benzyl, phenethyl, 3-phenylpropyl, C_1-C_6 aliphatic acyl groups, cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cyclopropylacetyl, cyclobutylacetyl, cyclopentylacetyl, cyclohexylacetyl, 3-cyclopentylpropionyl, 3-cyclohexylpropionyl, 4-cyclopentylbutyryl, 4-cyclohexylbutyryl, benzoyl, l-naphthoyl, 2-naphthoyl groups, phenylacetyl, l-naphthylacetyl, 3-phenylpropionyl, hydratropoyl, cinnamoyl, phenylpropioloyl, furoyl, thenoyl, nicotinoyl, isonicotinoyl, 4-thiazolecarbonyl, 5-pyrimidinecarbonyl, 2-pyrazinecarbonyl, 2-thienylacetyl, 3-(2-thienyl)propionyl, 4-thiazolylacetyl, 2-pyridylacetyl, 4-pyridylacetyl, 5-pyrimidinylacetyl, 1-aziridinylacetyl, 1-azetidinylacetyl, 3-azetidinylacetyl, l-pyrrolidinylacetyl, 2-pyrrolidinylacetyl, 3-pyrrolidinylacetyl, 3-(2-pyrrolidinyl)-propionyl, piperidinoacetyl, 2-piperidinylacetyl, 4-piperidinylacetyl, morpholinoacetyl, l-aziridine-carbonyl, 1-azetidinecarbonyl, 3-azetidinecarbonyl, 1-pyrrolidinecarbonyl, 2-pyrrolidinecarbonyl, 3-pyrrolidinecarbonyl, 1-piperidinecarbonyl 2-piperidinecarbonyl, 4-piperidinecarbonyl, 4-morpholinecarbonyl, phenacyl group, sulpho group, C_1-C_6 alkoxysulphonyl groups, C_1-C_6 alkylsulphonyl groups, C_2-C_6 alkenylsulphonyl groups, C_2-C_6 alkynylsulphonyl groups, cyclo-propylsulphonyl, cyclobutylsulphonyl, cyclopentylsulphonyl, cyclohexylsulphonyl, cyclopropyl-methylsulphonyl, cyclobutylmethylsulphonyl, cyclopentylmethylsulphonyl, cyclohexylmethyl-sulphonyl, 2-cyclopentylethylsulphonyl, 2-cyclohexylethylsulphonyl, 3-cyclopentylpropyl-sulphonyl, 2-cyclopentylpropylsulphonyl, phenylsulphonyl, l-naphthylsulphonyl, 2-naphthyl-sulphonyl, benzylsulphonyl, phenethylsulphonyl, 3-phenylpropylsulphonyl, 2-phenylpropyl-sulphonyl, 2-thienylsulphonyl, 4-thiazolylsulphonyl, 2-pyridylsulphonyl, 4-pyridyl-sulphonyl, 2-thienylmethylsulphonyl, 3-(2-thienyl)propylsulphonyl, 4-thiazolylmethylsulphonyl, 2-pyridyl-methylsulphonyl, 4-pyridylmethylsulphonyl group, groups of the formula



wherein R^{10} represents a hydrogen atom or a C_1-C_4 alkyl group and R^{11} represents a hydrogen atom, allyloxycarbonyl, 2-methylallyloxycarbonyl, 2-chloroallyloxy-carbonyl, 2,2,2-trichloroethoxy-carbonyl, 2,2,2-tribromoethoxycarbonyl, p-nitro-benzyloxycarbonyl or o-nitrobenzyloxycarbonyl,

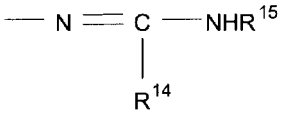
groups of the formula



wherein R^{12} and R^{13} are the same or different and each represents a hydrogen atom or a C_1-C_4 alkyl group and Y represents an oxygen atom, a sulphur atom or an imino group which may be optionally substituted with a C_1-C_4 alkyl group,

C_2-C_7 alkoxycarbonyl groups, benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl and o-nitrobenzyloxy carbonyl group; and

the substituents attached to the nitrogen atoms of the non-aromatic heterocyclic groups may be substituted with one or more groups selected from the group consisting of C_1-C_4 alkyl groups, C_1-C_4 alkoxy groups, hydroxy, amino, halogen, C_1-C_5 aliphatic acyloxy groups, C_1-C_5 aliphatic acylarnino groups, cyano, azido, carboxy, C_2-C_5 alkoxycarbonyl groups, the carbamoyl group, C_1-C_4 alkylthio group, C_l-C_4 alkylsulphinyl groups, C_1-C_4 alkylsulphonyl groups, nitro group, and groups of formula

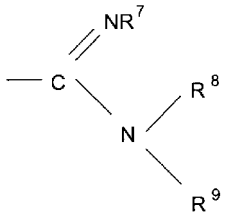


wherein R^{14} and R^{15} are the same or different and each represents a hydrogen atom or a C_1-C_4 alkyl group;

a substituted alkyl group, said substituted alkyl groups being selected from the group consisting of a hydroxyalkyl group, a protected hydroxy alkyl group, an aminoalkyl group, and a protected

aminoalkyl group;

a group represented by the formula



wherein R^7, R^8, and R^9 are the same or different and each represents hydrogen, methyl, ethyl, an amino-protecting group, or R^7 and R^8 or R^8 and R^9, together with the atom or atoms to which they are attached, form a ring and when R^8 and R^9 form a ring, they together represent ethylene, trimethylene, tetramethylene, when R^7 and R^8 form a ring, R^7 and R^8 together represent ethylene or trimethylene;

an aryl-substituted alkyl group, selected from the group consisting of benzyl, p-methoxybenzyl, m-nitrobenzyl, o-methylbenzyl, p-bromobenzyl and p-aminobenzyl; furfuryl;

an alkyl group having a non-aromatic heterocyclic substituent, the alkyl group of which is a C_1-C_4 alkyl, and the non-aromatic heterocyclic substituent is selected from the substituted or unsubstituted non-aromatic heterocyclic groups within the definition hereinbefore of R^4;

an alkenyl group or a substituted alkenyl group, selected from the group consisting of vinyl, allyl, 1-propenyl and 2-butenyl;

an alkynyl group or a substituted alkynyl group selected from the group consisting of ethynyl, 2-propynyl and 1-propynyl;

and when R^4 represents a substituted alkenyl or alkynyl group as defined above, the substituents are selected from the group consisting of the formula)$NR^{16}R^{17}$ wherein R^{16} and R^{17} are the same or different and each represents hydrogen, methyl, ethyl, propyl, isopropyl group, ormyl, acetyl, propionyl, isobutyryl, chloroacetyl, trifluoroacetyl, benzoyl group or an amino-protecting group; groups of the formula)$CONHR^{18}$, wherein R^{18} represents a hydrogen, methyl, ethyl, propyl, or an amino-protecting group; groups of the formula)$NHCONHR^{18}$; groups of the formula)$COOR^{19}$; wherein R^{19} represents hydrogen, methyl, ethyl, propyl or a carboxy-protecting group; groups of the formula)SR^{20}, wherein R^{20} represents hydrogen, methyl, ethyl, propyl, allyl, vinyl, 1-methylvinyl, 1-propenyl, ethynyl, 2-propynyl, 1-propynyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, 2-cyclohexylethyl, 2-cyclopentylethyl, benzyl, phenethyl, p-methoxybenzyl, p-bromobenzyl, phenyl, p-tolyl, p-methoxyphenyl, thienyl, furyl, imidazolyl, pyridyl, thienylmethyl, 2-thienylethyl, pyridylmethyl, imidazolylmethyl and thiazolymethyl; groups of the formula)$S(:0)R^{20}$; groups of the formula)SO_2R^{21} wherein R^{21}

represents any of the groups defined for R^{20} or methoxy, ethoxy or propoxy; groups of formula $)OSO_2R^{20}$; cyano; nitro; and azido groups;

R^5 represents hydrogen, or a carboxy-protecting group;

R^6 represents an alkoxy group having from 1 to 6 carbon atoms, or a phenoxy group selected from the group consisting of phenoxy, p-methylphenoxy, p-methoxyphenoxy groups, and a dialkylamino group wherein each alkyl group has from 1 to 6 carbon atoms, or two R^6 groups together represent an o-phenylenedioxy group, and the other R^6 represents any other R^6 group, or the three R^6 groups together represent a group of the formula $CH_3)(CH_2)0))_3$.